Immunomodulators, Asthma
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Interleukin-4 (IL-4) Antagonists		
dupilumab*,† (Dupixent®)[1]	Regeneron	Add-on maintenance treatment in patients with moderate-to-severe asthma ages ≥ 12 years with an eosinophilic phenotype or with oral corticosteroid-dependent asthma
Interleukin-5 (IL-5) Antagonists		
benralizumab* (Fasenra®, Fasenra Pen™)[2]	AstraZeneca	▪ Add-on maintenance treatment in patients with severe asthma ages ≥ 12 years, and with an eosinophilic phenotype
mepolizumab* (Nucala®)[3]	GlaxoSmithKline	▪ Add-on maintenance treatment in patients with severe asthma ages ≥ 6 years, and with an eosinophilic phenotype ▪ The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)
reslizumab* (Cinqair®)[4]	Teva Specialty	▪ Add-on maintenance treatment in patients with severe asthma ages ≥ 18 years, and with an eosinophilic phenotype
Anti-Immune Globulin E (IgE) Antibody		
omalizumab‡ (Xolair®)[5]	Genentech	▪ Moderate to severe persistent asthma in patients ≥ 6 years of age with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids ▪ Chronic idiopathic urticaria (CIU) in adults and adolescents ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment

* Benralizumab, dupilumab, mepolizumab, and reslizumab are not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

† Dupilumab, with or without topical corticosteroids, is indicated for the treatment of patients ages ≥ 6 years with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It is also indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). Detailed information regarding use for AD and nasal polyposis is discussed in other Therapeutic Class Reviews.

‡ Omalizumab is not indicated for other allergic conditions or other forms of urticaria and is not indicated for acute bronchospasm or status asthmaticus.

OVERVIEW

Asthma

Prevalence of asthma in the United States (US) continues to rise. An estimated 7.7% of adults and 7.5% of children (24.7 million Americans) have asthma with approximately 10% to 20% in poor control.[6,7] The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[8]

Asthma phenotypes have been identified by clinical and/or pathophysiological characteristics.[9] It has been established that eosinophils play a role in the inflammatory process of asthma and eosinophilic asthma is identified as a phenotype of asthma. Generally, patients with eosinophilic asthma have severe disease with high eosinophil levels in the blood and sputum despite treatment with a glucocorticoid.[10] Persistent levels of eosinophils in sputum may also be an indicator of disease severity.

The 2014 American Thoracic Society (ATS) and European Respiratory Society (ERS) Task Forces guidelines define severe asthma as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[11] The guidelines suggest a trial of omalizumab (Xolair) in adults and children aged 6 years and older with a confirmed IgE-dependent allergic asthma despite optimal drug and non-drug therapy. If there is no response within 4 months of beginning omalizumab, it is unlikely that continued treatment will be of benefit. Benralizumab (Fasenra), mepolizumab (Nucala), and reslizumab (Cinqair) were not available at the time that these guidelines were published.

The 2020 Global Initiative for Asthma (GINA) evidence-based report offers a management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects.[12] During this continuous cycle, a stepwise treatment approach is used to achieve control using the patient's current level of control as the baseline. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. According to GINA's stepwise approach, patients in steps 1 and 2 are considered to have mild asthma, patients in step 3 to 4, moderate asthma, and patients in steps 4 and 5, moderate to severe asthma. The 2020 GINA evidence-based report recommends that all adults and adolescents with asthma receive an ICS-containing controller medication. Due to the increased risk of severe exacerbations and asthma-related death, short-acting beta agonist (SABA)-only treatment is no longer recommended. For asthma adult patients and adolescents 12 years of age and older with mild symptoms (step 1 and step 2), the preferred treatment to control symptoms and prevent exacerbations are the following: an as-needed low dose ICS-formoterol (step 1) or daily low dose ICS (step 2). In patients whose asthma is uncontrolled on a low-dose ICS-containing controller despite good adherence and correct technique, a step up in treatment may be added (see tables below). Any step up in therapy should be re-assessed after 2 to 3 months; if there is not an adequate response, consider alternative treatment options or a referral. If asthma control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control.

Severe asthma is uncontrolled asthma despite adherence with optimized step 4 or step 5 treatment, correct inhaler technique, and proper management of contributory factors or asthma that worsens when high dose therapy is decreased.[13] If asthma is uncontrolled after 3 to 6 months on high dose ICS-LABA, it is recommended to refer to a specialist and phenotype into categories, such as severe allergic, aspirin-exacerbated, or eosinophilic asthma, as this may guide the selection of add-on treatment. Add-on treatments for severe asthma include tiotropium (Spiriva®), low-dose azithromycin (off-label), a leukotriene receptor antagonist (LTRA), a monoclonal antibody (benralizumab [Fasenra], mepolizumab [Nucala], omalizumab [Xolair], dupilumab [Dupixent]), a low-dose oral corticosteroid (OCS), bronchial thermoplasty, or sputum-guided therapy. Patients ≥ 6 years old with severe allergic asthma with elevated immunoglobulin E (IgE) levels may benefit from omalizumab (anti-IgE) therapy (Evidence A), those with severe eosinophilic asthma may benefit from benralizumab (≥ 12 years old), mepolizumab (≥ 6 years old), or reslizumab (≥ 18 years old) (anti-IL-5) therapy (Evidence A), those ≥ 12 years old with severe eosinophilic/Type 2 asthma or patients requiring maintenance OCS may benefit from dupilumab (anti-IL-4) therapy (Evidence A), and leukotriene receptor antagonists (LTRA) may be helpful for patients found to be aspirin sensitive (Evidence B).

Stepwise Approach to Asthma Control from 2020 GINA Guidelines – Controller Therapy[14]

Step	Age Group	Preferred Controller	Other Controller Options
Step 1: Symptom-driven or regular controller	≥ 12 years	▪ As-needed low dose ICS-formoterol (unlabeled indication)†	▪ Low dose ICS whenever SABA is taken (unlabeled indication)
	6 to 11 years	--	▪ Low dose ICS whenever SABA is taken (unlabeled indication) or daily low dose ICS
Step 2: One controller AND an as-needed reliever medication	≥ 12 years	▪ Low dose ICS or as needed low dose ICS-formoterol (unlabeled indication)†	▪ Leukotriene modifier or low dose ICS whenever SABA is taken (unlabeled indication)
	6 to 11 years	▪ Low dose ICS	▪ Leukotriene modifier or low dose ICS whenever SABA is taken (unlabeled indication)
Step 3: Two controllers and an as-needed reliever medication	≥ 12 years	▪ Low dose ICS/LABA	▪ Medium dose ICS OR low dose ICS + leukotriene modifier ▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis, house dust mite sensitivity, and FEV > 70% predicted
	6 to 11 years	▪ Low dose ICS/LABA or medium dose ICS	▪ Low dose ICS + leukotriene modifier
Step 4: Two controllers and an as-needed reliever medication	≥ 12 years	▪ Medium dose ICS/LABA	▪ High dose ICS, add-on tiotropium, or add-on leukotriene modifier ▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis, house dust mite sensitivity, and FEV > 70% predicted
	6 to 11 years	▪ Medium dose ICS/LABA; refer for expert advice	▪ High dose ICS/LABA, add-on tiotropium, or add-on leukotriene modifier
Step 5: Two controllers and an as-needed reliever medication	≥ 12 years	▪ High dose ICS/LABA; refer for phenotypic assessment with or without add-on therapy (e.g., tiotropium, anti-IgE [omalizumab], anti-interleukin-5[IL5]/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab])	▪ Add-on low dose oral corticosteroid, considering adverse effects
	6 to 11 years	▪ Refer for phenotypic assessment with or without add-on therapy (e.g., anti-IgE [omalizumab)	▪ Add-on anti-IL-5 or add-on low dose oral corticosteroid, considering adverse effects

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; IL-5 = interleukin-5; LABA = long acting $beta_2$-agonist; SABA = short acting $beta_2$-agonist

*Additional recommendations published regarding the assessment and treatment of severe asthma, incorporating other treatment modalities (e.g., tiotropium, anti-IgE [omalizumab], anti-IL5/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab], based on age)

† The data supporting the use of low-dose ICS/formoterol as a reliever medication are primarily derived from budesonide-formoterol.

Stepwise Approach to Asthma Control from 2020 GINA Guidelines (continued) – Reliever Therapy[15]

Age Group	Step	Preferred Reliever	Other Reliever Options
≥ 12 years	Steps 1 and 2	▪ As-needed low dose ICS-formoterol (unlabeled indication)†	▪ As needed SABA
	Steps 3 through 5	▪ As-needed low dose ICS-formoterol (unlabeled indication)‡	
6 to 11 years	Steps 1 through 5	▪ As needed SABA	--

ICS = inhaled corticosteroid; SABA = short acting beta$_2$-agonist

*Additional recommendations published regarding the assessment and treatment of severe asthma, incorporating other treatment modalities (e.g., tiotropium, anti-IgE [omalizumab], anti-IL5/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab], based on age)

† The data supporting the use of low-dose ICS/formoterol as a reliever medication are primarily derived from budesonide-formoterol.

‡ Low dose ICS-formoterol is reliever for those prescribed budesonide-formoterol or beclomethasone dipropionate-formoterol maintenance and reliever therapy.

Chronic Idiopathic Urticaria

The prevalence of chronic urticaria (CU) is estimated to be 0.5% to 5% of the general population.[16] Chronic urticaria is defined as episodic or daily hives lasting for 6 weeks or more that impairs quality of life. Main subtypes are chronic idiopathic urticaria (CIU) and inducible (physical) urticaria.[17] Chronic urticaria may be associated with presence of mononuclear cells (CD4+ Th1 and Th2 lymphocytes), eosinophils, neutrophils, basophils, mast cells, and activated macrophages. In 2014, a Joint Task Force for the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology (JCAAI) 2014 updated practice parameters for acute and chronic urticaria (CU).[18] Diagnosis of CU is based on history and physical examination. Typically, CU presents as pruritic edematous red wheals of variable size and shape with surrounding erythema. The majority of cases of CU have an undetermined cause (idiopathic); however, infectious and autoimmune conditions can be associated with CU.[19]

The AAAAI/ACAAI/JCAAI recommend a stepwise approach to care is recommended for chronic urticaria.[20] Treatment should begin based on the patient's level of severity and previous treatment history. At each level, medications should be evaluated for efficacy and patient tolerance. Once consistent control is achieved, a step-down in treatment may be considered. In step 1, monotherapy with second-generation antihistamines is considered first-line for CU in addition to avoidance of triggers (e.g., nonsteroidal anti-inflammatory drugs, food allergens) and relevant physical factors. If CU is not controlled, the antihistamine dose can be increased (if appropriate for the particular agent) or one of the following can be added: another second-generation or a first-generation antihistamine, a histamine-2 antagonist, or an LTRA (step 2). If control is still not achieved, dose advancement of a potent antihistamine (e.g. hydroxyzine or doxepin) may be considered, as tolerated (step 3). For CU that is refractory to maximal antihistamine therapy in step 3, alternative agents such as omalizumab or cyclosporine can be used; other anti-inflammatory, immunosuppressant, or biologic agents may be considered, but have a lower level of supporting evidence.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a systemic vasculitis of small-to-medium vessels, characterized by allergic rhinitis, asthma, and hypereosinophilia.[21,22,23] EGPA is a rare disease state affecting 1 to 3 out of 100,000 patients, with a higher incidence of about 1 per 15,000 in patients with asthma. Onset may occur between 15 and 70 years of age, but diagnosis is typically made between 35 and 50 years of age.[24,25] While the direct cause of the disease is unknown, HLA-DRB4 positivity may be a genetic risk factor.[26] Symptoms can vary from mild to life-threatening.[27]

Diagnosis of EGPA is based on symptoms, laboratory tests, imaging studies, physical examination, and biopsy of affected tissues to determine severity of vasculitis.[28] A diagnosis may be confirmed if in addition to vasculitis, patients also have at least 4 of the following features: asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and eosinophilic vasculitis.[29] Scoring systems to assess the severity of vasculitis and guide initial therapy in patients with EGPA include the 5-factor score (FFS) and the Birmingham Vasculitis Activity Score (BVAS).[30] The FFS ranges from 0 to 2, and attributes a point for one of the following and 2 points if 2 or more of the following are met: age > 65 years, cardiac insufficiency, gastrointestinal involvement, renal insufficiency, and ear/nose/throat manifestations. The BVAS has historically been used to a greater extent in research than clinical practice and includes general symptoms in addition to organ involvement. BVAS can range from 0 to 68 with 1 point being allotted for persistent symptoms and 2 points for new or worsening symptoms.

No US guidelines are currently available for the treatment of EGPA. As a consensus, EGPA that is not severe in nature is often treated with oral corticosteroids alone, and more than 90% of patients achieve remission.[31,32] Initial therapy may also include cyclophosphamide for patients with severe, multi-organ disease. Patients with severe EGPA may be transitioned to maintenance therapy with azathioprine, methotrexate, or leflunomide; evidence supporting their use is limited. Other treatments include anti-IL-5 antibodies such as mepolizumab, immunoglobulins, interferon-alpha, rituximab, or inhaled glucocorticoids.[33,34] Notably, mepolizumab is the only US Food and Drug Administration (FDA)-approved medication for this disease state.

PHARMACOLOGY[35,36,37,38,39,40]

Generally, eosinophils circulate in the peripheral blood and are found in peripheral tissue and respiratory mucosa, and levels increase in the presence of acute inflammation. Eosinophils are recruited into the airway in allergic asthma by the action of cytokines and chemokines, such as interleukin-5 (IL-5), a potent eosinophil activator that facilitates recruitment into tissues.

Benralizumab (Fasenra), mepolizumab (Nucala), and reslizumab (Cinqair) are IL-5 antagonists. They block IL-5 from binding to eosinophils, resulting in the inhibition of eosinophil growth and differentiation, recruitment, activation, and survival. While the exact mechanism of action for asthma has not been established, it is known that dupilumab (Dupixent) binds to interleukin-4-receptor alpha (IL4Rα) thereby inhibiting interleukin (IL)-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. Omalizumab (Xolair) is a recombinant humanized monoclonal anti-IgE antibody. In the treatment of asthma, omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils, this in turn decreases the release of allergic response mediators.

Approximately 30% to 50% of patients with chronic urticaria produce specific immunoglobulin G (IgG) antibodies against the FcεRIa subunit component of the high-affinity immunoglobulin E (IgE) receptor, and approximately 5% to 10% produce immunoglobulin G (IgG) antibodies against immunoglobulin E (IgE). The mechanism for which omalizumab influences chronic urticaria is not fully understood; it, however, reduces the number of FcεRI receptors on basophils and reduces free IgE levels, which have been associated with reduced basophil and mast cell activation.

PHARMACOKINETICS[41,42,43,44,45]

Drug	Half-Life (days)	Metabolism	Time to Peak Concentration (days)
Interleukin-4 (IL-4) Antagonists			
dupilumab (Dupixent)	nr*	N/A*	7
Interleukin-5 (IL-5) Antagonists			
benralizumab (Fasenra)	15.5	Enzymatic proteolysis	nr
mepolizumab (Nucala)	16-22	Enzymatic proteolysis	nr
reslizumab (Cinqair)	24	Enzymatic proteolysis	End of infusion
Anti-Immune Globulin E (IgE) Antibody			
omalizumab (Xolair)	24-26	N/A†	7-8

nr = not reported

* The metabolic pathway of dupilumab has not been established, but is expected to be degraded through the same catabolic pathways as endogenous IgG forming small peptides and amino acids. After the last steady-state dose of 300 mg every 2 weeks, 300 mg once weekly, or 200 mg every 2 weeks regimens, the median times to non-detectable concentration (<78 ng/mL) of dupilumab are 10 to 12, 13, and 9 weeks, respectively.

† No formal drug metabolism studies were conducted.[46]

CONTRAINDICATIONS/WARNINGS[47,48,49,50,51]

Agents in this review are contraindicated in patients with a known hypersensitivity to any component of the product.

Omalizumab (Xolair) and reslizumab (Cinqair) carry boxed warnings regarding anaphylaxis. Anaphylaxis has been reported to occur after the first dose and up to 1 year after beginning omalizumab treatment; time to onset of the reaction was reported 90 to 120 minutes after administration. Anaphylaxis has been reported during reslizumab infusion and up to 20 minutes after infusion completion. Although the labels for benralizumab (Fasenra) and mepolizumab (Nucala) do not contain a boxed warning, hypersensitivity reactions can occur within hours to days of the dosage being given. Omalizumab and reslizumab should only be administered in a healthcare setting by a healthcare professional (HCP); patients should be closely monitored for an appropriate time period after administration of the dose.

Although benralizumab and mepolizumab should also be used under the guidance of a HCP and monitoring following administration is recommended, these products are available as prefilled autoinjectors (both products) and a prefilled syringe (mepolizumab only) for patient/caregiver administration following appropriate assessment and training by an HCP. The prefilled syringe formulation of benralizumab continues to require administration by a HCP, as does the vial preparation of mepolizumab. Dupilumab (Dupixent) labeling also contains a warning for hypersensitivity. In clinical

trials for asthma, one patient treated with dupilumab experienced anaphylaxis. Dupilumab is intended for use under the guidance of an HCP and may be self-administered with proper training using the prefilled syringe.

None of the agents within this class should be used to treat acute asthma symptoms or asthma exacerbations.

Herpes zoster has been reported more often in patients treated with mepolizumab than with placebo. Varicella vaccination may be considered prior to starting therapy.

In clinical trials for asthma, conjunctivitis and keratitis were reported at similar rates with dupilumab and placebo; however, a higher incidence of both conditions was reported in atopic dermatitis trials in patients treated with dupilumab compared to placebo. Patients should be advised to consult their healthcare provider if new onset or worsening eye symptoms develop.

When appropriate, gradually reduce dosages of systemic or inhaled corticosteroids; avoid abrupt discontinuation or dose reductions.

Pre-existing helminth infections should be treated prior to initiating asthma immunomodulator therapy, since it may reduce the immunological response to some helminth infections. If patients become infected while receiving treatment with benralizumab, mepolizumab, or reslizumab and do not respond to anti-helminth treatment, discontinue treatment with the anti-IL-5 agent until infection resolves. Response to anti-helminth treatment does not appear to be affected by omalizumab.

In placebo-controlled trials, malignant neoplasm was reported in 0.6% of patients treated with reslizumab (compared to 0.3% with placebo) and in 0.5% of patients treated with omalizumab (compared to 0.2% with placebo). Long-term studies to evaluate the carcinogenicity of mepolizumab have not been performed; risk is unknown.

DRUG INTERACTIONS[52,53,54,55,56]

The use of live vaccines should be avoided in patients taking dupilumab (Dupixent).

There have been no formal drug interaction studies conducted with benralizumab (Fasenra), mepolizumab (Nucala), omalizumab (Xolair), and reslizumab (Cinqair).

ADVERSE EFFECTS[57,58,59,60,61]

Drug	Arthralgia	Headache	Fatigue	Injection Site Reaction	Pruritus	Nasopharyngitis
Interleukin-4 (IL-4) Antagonists						
dupilumab (Dupixent)	nr*	nr	nr	Asthma: 14-18 (6)	nr	nr
Interleukin-5 (IL-5) Antagonists						
benralizumab (Fasenra)	nr	8-8.2 (5.3-6)	nr	2.2 (1.9)	nr	5† (3)
mepolizumab (Nucala)‡	nr	19 (18)	5 (4)	8-15 (3-13)	2-3 (2-3)	≥ 3
omalizumab (Xolair)	Asthma: 8 (6) CIU: 2.9 (0.4)	Asthma: Aged ≥ 12 years – 15; 6 to < 12 years – 0.2 CIU: 6.1-12 (2.9)	Asthma: 3 (2)	45 (43)	Asthma: 2 (1)	Asthma: 2 (1) CIU: 6.6-9.1 (7)
Anti-Immune Globulin E (IgE) Antibody						
reslizumab (Cinqair)	nr	nr	nr	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported

* While arthralgia was not reported in dupilumab studies for asthma, it was reported in studies for CRSwNP (3% with dupilumab versus 2% with placebo).

† Reported as pharyngitis.

‡ Adverse reaction profile for subjects 6 to 11 years of age was similar to that observed in subjects aged 12 years and older.

Other adverse effects reported with benralizumab (Fasenra) not indicated above include hypersensitivity reactions (e.g., urticaria), which occurred 3% in both placebo and treatment groups, and pyrexia, which occurred in 2.7% to 3% of patients treated with benralizumab compared to 1.3% to 2% of patients treated with placebo.

Other adverse effects reported with dupilumab (Dupixent) in patients with asthma were oropharyngeal pain (2%) and eosinophilia (2%).

Common adverse reactions reported for mepolizumab (Nucala) with an incidence greater than placebo include: headache (19% versus 18%), injection site reaction (8% versus 3%), back pain (5% versus 4%), fatigue (5% versus 4%) eczema (3% versus < 1%), and muscle spasms (3% versus < 1%). No additional adverse reactions were noted in the EPGA study. However, 4% of patients receiving 300 mg every 4 weeks for EPGA experienced systemic hypersensitivity reactions including rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor; compared to 1% of patients in the placebo group.

Many adverse reactions reported with omalizumab (Xolair) were infectious in nature, including nasopharyngitis, sinusitis, upper respiratory tract infection (including viral) pharyngitis streptococcal, otitis media, viral gastroenteritis, and arthropod bites. Generalized pain, arthralgia, pain of the leg, arm, ear, upper abdomen and headache were also reported. Injection site reactions occurred in 45% of patients treated with omalizumab compared to 43% treated with placebo.

In a 5-year observational cohort study in asthmatic patients (≥ 12 years of age) a higher rate of overall cardiovascular and cerebrovascular serious adverse events was reported in patients treated with omalizumab (13.4/1,000 patient-years) compared to non-omalizumab-treated patients (8.1/1,000 patient-years). Rates of transient ischemic attack, myocardial infarction, pulmonary hypertension, and venous thrombosis/pulmonary embolism were at least 2-fold greater in omalizumab-treated patients; the incidence of ischemic stroke and cardiovascular death were similar between cohorts. However, a pooled analysis of 25 randomized double-blind, placebo-controlled trials of up to 52 weeks in duration could not confirm or reject the conclusion of the observational study due to limitations such as shorter study duration and lower number of events reported.

In clinical studies, oropharyngeal pain occurred more often in patients treated with reslizumab (Cinqair) than those who received placebo (2.6% versus 2.2%). Musculoskeletal adverse reactions were reported on the day of infusion in 2.2% and 1.5% of patients treated with reslizumab and placebo, respectively. Elevated creatinine phosphokinase (CPK), including levels greater than 10 times the upper limit of normal, were reported, but were asymptomatic and did not lead to treatment discontinuation.

As with all therapeutic proteins, there is a potential for immunogenicity with the products in this review. In clinical trials, 13% of patients treated with benralizumab (12% considered neutralizing antibodies), 9% of patients with asthma treated with dupilumab (4% with neutralizing antibodies), and 4.8% to 5.4% of patients treated with reslizumab developed anti-drug antibodies (ADA). In clinical trials with mepolizumab for asthma and EGPA, 6% and < 2% of patients, respectively, developed ADAs. No impact of ADAs on clinical efficacy was observed for benralizumab, mepolizumab, or reslizumab. ADA to omalizumab were detected in < 0.1% of asthmatic patients > 12 years of age treated with omalizumab; data were not sufficient to draw any relevant conclusions.

SPECIAL POPULATIONS[62,63,64,65,66]

Pediatrics

Safety and efficacy have not been established for benralizumab (Fasenra) or dupilumab (Dupixent) in patients younger than 12 years of age or for reslizumab (Cinqair) in patients younger than 18 years for the treatment of asthma. Mepolizumab (Nucala) and omalizumab (Xolair) are indicated for use in patients 6 years and older to treat asthma; safety and efficacy for treatment of asthma in patients younger than this have not been established. Safety and efficacy for the use of mepolizumab for conditions other than asthma have not been established in pediatrics. Omalizumab is also indicated for the treatment of CIU in patients 12 years and older; its safety and efficacy in treating CIU in those younger than 12 years have not been established.

Pregnancy

Clinical data on use of benralizumab, mepolizumab, and reslizumab during pregnancy are insufficient to inform on drug-associated risks. Potential fetal risks may be greater during the second and third

trimesters of pregnancy as monoclonal antibodies can cross the placenta as pregnancy progresses. No fetal harm has been detected in animal studies.

Drug-associated risk of maternal or fetal harm have not been detected in the available data with dupilumab use in pregnant women; enrollment in the pregnancy registry for dupilumab is encouraged.

A prospective cohort registry study in pregnant women exposed to omalizumab showed no increase in the incidence of major birth defects or miscarriage. The risk of low birth weight infants was increased; however, pregnant women taking omalizumab had more severe asthma, which may have contributed.

Increased risk of preeclampsia in the mother and neonates born prematurity, with low birth weight, and small for gestational age have been reported in pregnant women with poorly or moderately controlled asthma. Asthma control should be closely monitored during pregnancy and adjustments made to maintain optimal control.

There is an ongoing registry that monitors pregnancy outcomes in women treated for asthma with benralizumab and mepolizumab. Healthcare providers (or the patient) are encouraged to enroll their patient.

Geriatrics

No differences in safety or efficacy were seen in patients ≥ 65 years old treated with benralizumab or reslizumab compared to younger patients; however, a greater sensitivity in some individuals cannot be ruled out. In clinical trials for asthma, no differences in safety or efficacy were detected between patients aged ≥ 65 years and younger patients who were treated with dupilumab. There were insufficient numbers of patients ≥ 65 years old in clinical studies of mepolizumab and omalizumab to identify differences in response from younger populations.

Renal and Hepatic Impairment

No pharmacokinetic studies have been performed to assess the impact of renal or hepatic impairment on benralizumab, dupilumab, mepolizumab or reslizumab. Renal and hepatic impairment are not addressed in the omalizumab label.

DOSAGES[67,68,69,70,71]

Drug	Dose	Dosage/Administration Comments	Dosage Forms
Interleukin-4 (IL-4) Antagonists			
dupilumab (Dupixent)	Asthma (adults and adolescents ≥ 12 years of age): ▪ Initial dose of 400 mg (two 200 mg injections) followed by 200 mg every other week; or ▪ Initial dose of 600 mg (two 300 mg injections) followed by 300 mg every other week	For subcutaneous (SC) use only; may be given in the thigh, abdomen, or upper arm The 600 mg initial and 300 mg maintenance regimen is recommended for patients with oral corticosteroid-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated	200 mg/1.14 mL and 300 mg/2 mL SDP syringes; 300 mg/ 2 mL pre-filled pen
Interleukin-5 (IL-5) Antagonists			
benralizumab (Fasenra, Fasenra Pen)	30 mg SC every 4 weeks for 3 doses, followed by 30 mg once every 8 weeks thereafter	For SC use only (upper arm [HCP administration only], thigh, abdomen) The SDP syringe should only be administered by an HCP; the autoinjector (pen) can be administered by the patient or a caregiver	30 mg/mL solution in a SDP syringe; 30 mg/mL solution in SDP autoinjector
mepolizumab (Nucala)	Asthma: adults and adolescents ≥ 12 years of age: 100 mg SC every 4 weeks Asthma children 6 to 11 years of age: 40 mg SC every 4 weeks EPGA (adult): 300 mg SC every 4 weeks as 3 separate 100 mg injections spaced at least 5 cm apart	For SC use only; administer in the upper arm, thigh, or abdomen The vial for reconstitution should only be administered by an HCP The prefilled autoinjector and prefilled syringe can be administered by the patient or a caregiver	100 mg lyophilized powder for injection in a SDV; 100 mg/mL solution in a SDP autoinjector and SDP syringe
reslizumab (Cinqair)	3 mg/kg every 4 weeks by intravenous (IV) infusion over 20 to 50 minutes	For IV infusion only; do not administer via IV push or bolus Should only be administered in a healthcare setting by an HCP who can manage anaphylaxis Discontinue infusion immediately if anaphylaxis occurs	100 mg/10 mL solution in SDV
Anti-Immune Globulin E (IgE) Antibody			
omalizumab (Xolair)	**Asthma:** 75 mg to 375 mg SC every 2 or 4 weeks Dose and frequency is determined by serum total IgE level before the start of treatment, and body weight, as instructed in the package insert **CIU:** 150 mg to 300 mg SC every 4 weeks Dosing is not dependent on serum IgE or body weight	For SC use only (upper arm, thigh) Should only be administered in a healthcare setting by an HCP who can manage anaphylaxis The lyophilized powder for injection may take 5 to 10 seconds to administer due to the solution viscosity Doses > 150 mg should be divided among more than one injection site; do not administered > 150 mg per site	150 mg lyophilized powder for injection in a SDV; 75 mg/0.5 mL and 150 mg/1 mL solution in a SDP syringe

SDP = single-dose, prefilled; SDV = single-dose vial

Reslizumab and omalizumab should only be administered in a healthcare setting by a HCP; patients should be closely monitored for an appropriate time period after administration of the dose. In April of 2020, the FDA allowed for the *temporary* self-administration of the prefilled syringe (PFS) during the COVID-19 pandemic for omalizumab.[72] Since patients with moderate to severe asthma are considered high-risk for severe COVID-19 related illness, HCPs are to determine those patients who are able to self-administer depending on local pandemic guidelines and restrictions, as well as patient parameters. The manufacturer has provided criteria to assist HCPs in determining appropriate patients; the criteria are detailed in their published communication. Patients or caregivers can administer benralizumab, dupilumab, or mepolizumab using the prefilled autoinjector (benralizumab and mepolizumab), prefilled pen (dupilumab), or prefilled syringe (dupilumab and mepolizumab) following proper training if an HCP determines it to be appropriate. The vial preparation of mepolizumab requires reconstitution and administration by an HCP; the prefilled syringe formulation of benralizumab also requires administration by an HCP. In general, patients receiving benralizumab or mepolizumab should also be monitored following administration.

Total IgE levels remain elevated during treatment and for up to 1 year after therapy discontinuation of omalizumab. If therapy is interrupted for more than 1 year, retest total serum IgE level to determine dosage. For interruptions less than 1 year in duration, the dosage may be based on the original baseline serum IgE levels.

The need for continued therapy of agents in this class should be reassessed periodically based on current disease severity and asthma control.

Benralizumab, dupilumab, omalizumab, and reslizumab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Benralizumab prefilled syringe and autoinjector can be stored at room temperature (≤ 25°C [77°F]) for up to 14 days in the original carton, after which time the product must be used or discarded. Likewise, dupilumab may be kept at room temperature for up to 14 days, after which time the product must be used or discarded. Omalizumab lyophilized powder should be shipped at controlled ambient temperature (≤ 30°C [≤ 86°F]). Mepolizumab vials should be stored at temperatures below 25°C (77°F); mepolizumab prefilled syringes and prefilled autoinjectors should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) prior to and following dispensing. If required, an unopened carton may be stored at up to 30°C (86°F) for a maximum of 7 days. The prefilled syringe and prefilled autoinjectors should be placed at room temperature for 30 minutes prior to administration; these are required to be used within 8 hours of being removed the carton.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Placebo-controlled trials are included when no comparative trials are available. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including

those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

benralizumab (Fasenra) versus placebo

SIROCCO: A multinational, randomized, double-blind, parallel-group, placebo-controlled study compared the efficacy of benralizumab to placebo in patients with severe asthma (n=1,205).[73] Eligible patients, which included those ages 12 to 75 years with a diagnosis of asthma ≥ 1 year and ≥ 2 exacerbations while on ICS plus LABA in the previous year, were randomly assigned 1:1:1 to SC benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first 3 doses every 4 weeks) or placebo Q4W for 48 weeks as add-on to their standard treatment. Patients were stratified based on blood eosinophil counts. Compared with placebo, both benralizumab dosing regimens reduced the annual asthma exacerbation rate over 48 weeks, the primary endpoint (Q4W rate ratio, 0.55 [95% CI, 0.42 to 0.71; p<0.0001]; Q8W rate ratio, 0.49 [95% CI, 0.37 to 0.64; p<0.0001]). A benefit versus placebo was also seen in notable secondary endpoints, including pre-bronchodilator FEV_1 and asthma symptoms (Q8W regimen only).

CALIMA: Another multinational, randomized, double-blind, parallel-group, placebo-controlled study compared the efficacy of benralizumab to placebo in patients with severe asthma (n=1,306).[74] Eligible patients, which included those ages 12 to 75 years and ≥ 2 exacerbations while on ICS plus LABA in the previous year, were randomly assigned 1:1:1 to SC benralizumab 30 mg either Q4W or Q8W (first 3 doses every 4 weeks) or placebo Q4W for 56 weeks as add on to their standard treatment. Patients were stratified based on blood eosinophil counts. Compared with placebo, both benralizumab dosing regimens reduced the annual asthma exacerbation rate over 56 weeks, the primary endpoint (Q4W rate ratio, 0.64 [95% CI, 0.49 to 0.85; p=0.0018]; Q8W rate ratio, 0.72 [95% CI, 0.54 to 0.95; p=0.0188]). As seen in the SIROCCO trial above, a benefit versus placebo was also seen in key secondary endpoints, including pre-bronchodilator FEV_1 and asthma symptoms (Q8W regimen only).

ZONDA: A 28-week, multinational, randomized, placebo-controlled trial assessed the impact of benralizumab versus placebo on the reduction in the oral glucocorticoid dose (while maintaining asthma control) in adult patients with severe asthma (n=220).[75] Eligible patients were randomized to SC benralizumab 30 mg either Q4W or Q8W (first 3 doses every 4 weeks) or placebo Q4W. Both benralizumab dosing regimens significantly reduced the percentage change in the oral glucocorticoid dose from baseline to week 28, the primary endpoint (75% reduction for both active treatments versus 25% with placebo; p<0.001 for both comparisons). Both benralizumab groups also resulted in a lower rate of annual exacerbations compared to placebo (Q4W: 55% lower [marginal rate, 0.83 versus 1.83, respectively; p=0.003]; Q8W: 70% lower [marginal rate, 0.54 versus 1.83, respectively; p<0.001]). However, a statistically significant difference versus placebo was not found in FEV_1, and results were mixed in other secondary endpoints.

BISE: A multinational, randomized, double-blind, placebo-controlled study assessed the impact of benralizumab on lung function in adults with asthma (n=211).[76] Eligible patients included those with a postbronchodilator reversibility in FEV_1 ≥ 12% at screening receiving either low- to medium-dosage ICS or low-dosage ICS/LABA with a morning pre-bronchodilator FEV_1 of ≥ 50% to 90% predicted and ≥ 1 of

the following symptoms at screening: a daytime or night-time asthma symptom score ≥ 1 for ≥ 2 days, rescue SABA use for ≥ 2 days, or night-time awakenings due to asthma ≥ 1 night. All patients received standardized converted budesonide and were then assigned to either placebo or benralizumab SC 30 Q4W for 12 weeks. Treatment with benralizumab resulted in an 80 mL improvement in pre-bronchodilator FEV_1 after 12 weeks versus placebo, the primary endpoint (95% CI, 0 to 150; p=0.04).

dupilumab (Dupixent) versus placebo

LIBERTY ASTHMA QUEST: This study enrolled 1,902 patients ≥ 12 years of age with uncontrolled moderate-to-severe asthma who were on a medium or high-dose inhaled corticosteroid (ICS) and 1 to 2 additional controller medications.[77,78] Patients were randomized to add-on therapy with dupilumab 200 mg or 300 mg SC every 2 weeks (following initial doses of 400 mg and 600 mg, respectively) or matching placebo for 52 weeks. Treatment with the dupilumab 200 mg and 300 mg regimens resulted in a lower adjusted annualized rate of severe asthma exacerbations (coprimary endpoint) compared to placebo, by 47.7% and 46%, respectively (p<0.001 for both), at 52 weeks. Prespecified subgroup analyses showed a significant difference in exacerbation rates with either dose of dupilumab compared to placebo among patients with an eosinophil count of ≥ 300 mm^3, but not in patients with eosinophil count < 150 mm^3. In the overall trial population, the change from baseline in the FEV_1 before bronchodilator use at week 12 (the other coprimary endpoint) was 0.32 L with dupilumab 200 mg versus 0.18 L with matching placebo (difference, 0.14 L; p<0.001) and 0.34 L with dupilumab 300 mg versus 0.21 L with matching placebo (difference, 0.13 L; p<0.001).

LIBERTY ASTHMA VENTURE: This 24-week trial enrolled 210 patients ages ≥12 years with asthma on daily oral corticosteroids (OCS) and regular use of high-dose ICS plus an additional controller.[79,80] Patients were randomized to add-on therapy with dupilumab 300 mg or matching placebo SC every 2 weeks for 24 weeks. The background OCS dose was titrated downward every 4 weeks during weeks 4 to 20, as long as asthma control was maintained. The change in OCS dose from baseline at week 24 (primary endpoint) was -70.1% with dupilumab and -41.9% with placebo (p<0.001). In the dupilumab group 80% of patients experienced at least a 50% reduction in OCS dose and 48% were able to discontinue OCS therapy compared 50% and 25%, respectively in the placebo group. In addition, dupilumab treatment resulted in a greater reduction in OCS dose compared to placebo, regardless of the baseline blood eosinophil count.

mepolizumab (Nucala) versus placebo

MENSA: A 32-week placebo-controlled trial randomized 576 patients, ages 12 to 82 years, with recurrent asthma exacerbations and evidence of eosinophilic inflammation to receive mepolizumab 75 mg intravenously (IV), mepolizumab 100 mg subcutaneously (SC), or placebo every 4 weeks.[81] Adult patients enrolled had a forced expiratory volume in 1 second (FEV_1) < 80% predicted; patients 12 to 18 years had FEV_1 < 90% predicted or FEV_1 to forced vital capacity (FVC) ratio < 0.8. Background therapy was continued. Patients had either a peripheral blood eosinophil count ≥ 150 cells/µL at screening or ≥ 300 cells/µL at some time during the previous year. The study reported a reduction in the primary endpoint, rate of exacerbations, by 47% (95% confidence interval [CI], 28 to 60) in those treated with IV mepolizumab and 53% (95% CI, 36 to 65) in those treated with SC mepolizumab, both as compared to placebo (p>0.001, for both). Emergency department or hospitalization due to asthma exacerbation was 32% less with IV mepolizumab and 61% less with SC mepolizumab, each as compared to placebo. By study end the mean increases over placebo in the secondary endpoints for IV and SC mepolizumab were as follows: FEV_1, - 100 mL and 98 mL, respectively; St George's Respiratory Questionnaire (SGRQ),

-6.4 and 7 points, respectively; and improvement in asthma control questionnaire (ACQ-5), -0.42 and 0.44 points, respectively (p<0.001 for all comparisons). Mepolizumab by the IV route is not FDA-approved.

SIRIUS: A 24-week double-blind, placebo-controlled steroid-reduction study randomized 135 patients (≥ 12 years of age) with severe asthma with eosinophilic inflammation to mepolizumab 100 mg SC or placebo once every 4 weeks.[82,83] The study included 4 phases. Phase 1 was the oral corticosteroid (OCS) optimization phase that titrated patients to the lowest OCS dose to maintain asthma control and lasted 3 to 10 weeks. Mepolizumab and placebo were initiated during the 4-week phase 2. In the 16-week phase 3, doses of OCS were titrated according to a recommended schedule. Phase 4 was a 4-week maintenance phase in which no further OCS titration was made. Patients had either a peripheral blood eosinophil count ≥ 150 cells/µL during the optimization phase or ≥ 300 cells/µL during the 12 months prior to screening. Compared with placebo, patients in the mepolizumab group achieved greater reductions in daily maintenance OCS dose, while maintaining asthma control. Twenty-three percent of mepolizumab patients versus 11% placebo patients had a 90% to 100% OCS dose reduction; 17% versus 8%, respectively, had a reduction of 70% to < 90%. The median percentage reduction from baseline in OCS dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group (p=0.007).

COSMEX: A 52-week, open-label, extension study that included 340 patients from SIRIUS and MENSA with life-threatening/seriously debilitating asthma did not identify new safety signals; it reported a clinically significant exacerbation rate of 0.93 events/year (95% CI, 0.81 to 1.06), an exacerbation requiring hospitalization or emergency department visit rate of 0.13 (95% CI, 0.1 to 0.18), and an exacerbation requiring hospitalization rate of 0.07 (95% CI, 0.05 to 0.1).[84]

MUSCA: A randomized, double-blind, placebo-controlled phase 3b trial enrolled 551 patients (≥ 12 years of age) with severe eosinophilic asthma and a history of ≥ 2 exacerbations, despite regular use of high-dose ICS plus other controller medicines that required treatment in the previous 12 months.[85] Patients received mepolizumab 100 mg or placebo SC every 4 weeks, in addition to standard of care, for 24 weeks. In the modified intent-to-treat population, mepolizumab versus placebo resulted in significant improvements at week 24 from baseline in SGRQ total score (least squares mean change from baseline -15.6 versus -7.9, a treatment difference of -7.7 (95% CI, -10.5 to -4.9; p<0.0001). Most common adverse effects with mepolizumab and placebo were headache (16% versus 21%, respectively) and nasopharyngitis (11% versus 17%, respectively).

The efficacy of mepolizumab for add-on therapy for severe asthma with eosinophilic phenotype in children 6 to 11 years of age has been extrapolated from efficacy studies in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety analyses.[86] An open-label clinical trial was conducted in 36 patients between the ages of 6 and 11 years old with severe asthma (mean age, 8.6 years; 31% female).[87] Subjects had a history of ≥ 2 exacerbations in the previous year despite treatment with medium or high-dose ICS plus additional controller medications with or without oral corticosteroids (OC) and had blood eosinophils of ≥ 150 cells/µL at screening or ≥ 300 cells/µL within the 12 months prior to enrollment. Based on the 12-week pharmacokinetic data from this trial, a dose of 40 mg every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC. An open-label extension study of 52 weeks (n=30) reported a safety profile similar to that seen in adults and adolescents.[88]

reslizumab (Cinqair) versus placebo

Two similar 52-week phase 3, double-blind, placebo-controlled trials included 953 patients 12 to 75 years of age with eosinophilic asthma as evident by a blood eosinophil count ≥ 400 cells/µL within the previous 3 or 4 weeks and at least 1 asthma exacerbation requiring systemic corticosteroid use in the past 12 months. Patients received IV reslizumab 3 mg/kg or placebo every 4 weeks.[89,90,91] Both studies reported a significant reduction in rate of asthma exacerbation. The point estimate for exacerbation rate ranged from 0.86 to 0.9 per year in reslizumab-treated patients versus 1.8 to 2.1 per year in placebo patients. In addition, mepolizumab reduced the rate of exacerbations requiring emergency department visit and/or hospitalization; however, the difference was not statistically significant.

A 16-week, phase 3, double-blind, placebo-controlled study included a total of 315 patients aged 12 to 75 years with eosinophilic asthma.[92,93,94,95] Patients had a blood eosinophil count ≥ 400 cells/µL. Patients were randomized to reslizumab 0.3 mg/kg or 3 mg/kg or placebo every 4 weeks. Maintenance OCS were not allowed. Primary endpoint was change in FEV_1 from baseline to week 16. Mean difference in change in FEV_1 between study drug and placebo was 115 mL for the lower dose of reslizumab and 160 mL for the higher dose. Reslizumab 0.3 mg/kg is not an FDA approved dosage.

A 16-week, phase 3, double-blind, placebo-controlled trial included 496 adults who were unselected for baseline serum eosinophil levels (approximately 80% of patients had eosinophil count < 400 cells/µL).[96,97,98,99] Patients were randomized to IV reslizumab 3 mg/kg or placebo every 4 weeks. Mean change in FEV_1 was 76 mL (95% CI, -6 to 158). A modest treatment effect was reported in patients with baseline eosinophil count < 400/µL (treatment difference=, 31 mL) and a larger effect for those with a baseline eosinophil count > 400/µL (treatment difference, 270 mL; p=0.0436). Due to the small number of patients in the eosinophil count > 400/µL cohort, interpretation of these results is limited.

A 24 month, open-label extension study evaluating long-term safety and efficacy of IV reslizumab 3 mg/kg given every 4 weeks, included 740 patients who received continuous exposure for at least 12 months and 249 patients with continuous exposure for at least 24 months.[100] The most common adverse effects experienced were worsening of asthma and nasopharyngitis. Serious adverse effects were experienced by 7% of patients, however only 2% discontinued due to these adverse effects. Over the course of treatment, patients maintained lung function and asthma control for up to 2 years.

omalizumab (Xolair) versus placebo

Two double-blind, placebo-controlled trials included patients 12 to 76 years of age with moderate to severe persistent asthma and a positive skin test to a perennial aeroallergen.[101] Patients were randomized to omalizumab based on body weight and baseline serum total IgE level according to pre-specified dosing instructions; maximum dose per 4 weeks was 750 mg. In studies 1 (n=525) and 2 (n=546), baseline FEV_1 was 40% to 80% predicted. During a run-in period, patients were converted to and stabilized on inhaled beclomethasone dipropionate. Long-acting beta-agonists (LABA) therapy was not allowed in this study. Patients receive omalizumab for 16 weeks, then entered a 12-week ICS dose-reduction phase. In studies 1 and 2 the mean number of exacerbations per patient was statistically significantly reduced with omalizumab compared to placebo. A reduction in asthma exacerbation was not observed in the omalizumab treated patients who had baseline FEV_1 > 80% predicted or in patients who required maintenance therapy with oral steroids.

A third double-blind, placebo-controlled trials included patients (n=341) 12 to 76 years of age with moderate to severe persistent asthma and a positive skin test to at least 1 perennial aeroallergen.[102]

During the run-in phase, patients were stabilized on fluticasone propionate. LABA therapy was allowed. Patients were randomized to omalizumab or placebo and were stratified by use of ICS-only or ICS plus oral steroids. After 16 weeks of omalizumab therapy, patients entered a 16-week ICS dose reduction phase. The number of exacerbations was similar for omalizumab and placebo groups. No reduction of asthma exacerbations was seen in patients who had a baseline FEV_1 > 80% predicted or in patients who required maintenance therapy with oral steroids.

A 52-week, placebo-controlled trial evaluated safety and efficacy of omalizumab therapy in 628 patients 6 to < 12 years of age with moderate to severe asthma, uncontrolled with ICS with or without other controller medications.[103] Patients had been diagnosed with asthma for at least 1 year and had positive skin tests for perennial aeroallergen. During the first 24 weeks, steroid doses were unchanged. At week 24, the rate of asthma exacerbations was statistically significantly lower for the omalizumab group compared to placebo (0.45 versus 0.634; rate ratio [RR], 0.69 [95% CI, 0.53 to 0.9]). During the next 28 weeks, adjustment of steroid doses was allowed. A reduced rate of asthma exacerbations was also observed with omalizumab during the entire 52-week study (0.78 versus 1.36; RR, 0.57 [95% CI, 0.45 to 0.72]). No significant difference was seen in nocturnal symptom scores, beta-agonist use, and FEV_1 between the omalizumab and placebo groups.

An additional 28-week double-blind, placebo-controlled study included 334 patients with moderate to severe asthma, 298 of which were 6 to < 12 years old.[104] Patients were well-controlled on ICS. Fewer asthma exacerbations were reported in the omalizumab group during the 16-week ICS fixed-dose period (0.18 versus 0.32; RR, 0.58 [95% CI, 0.35 to 0.96]) and the 28-week treatment period (0.38 versus 0.76; RR, 0.5 [95% CI, 0.36 to 0.71]).

Chronic Idiopathic Urticaria

omalizumab (Xolair) versus placebo

Two placebo-controlled, multiple-dose trials evaluated the safety and efficacy of omalizumab in adults and adolescents with CIU. Trial 1 was 24 weeks duration (n=319), while trial 2 was 12 weeks (n=322).[105] Omalizumab SC 75 mg, 150 mg, or 300 mg or placebo were added to the patients baseline H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week observation period. Urticaria activity scores (UAS7) was measured weekly. Baseline UAS7 ranged between 13.7 and 14.5. In trial 1, more patients treated with omalizumab 300 mg (36%) reported no itch or hives (UAS7=0) compared to omalizumab 150 mg (15%) omalizumab, 75 mg (12%), and placebo (9%). In both trials, omalizumab 150 mg and 300 mg were associated with greater reductions in itch severity scores (-2.95 [95% CI, -4.72 to -1.18] and -5.8 [95% CI, -7.49 to -4.1], respectively) and hive count scores (-3.44 [95% CI, -5.57 to -1.32] and -6.93 [95% CI, -9.1 to -4.76], respectively) compare to placebo at week 12; similar findings were reported at the end of trial 2. Omalizumab 75 mg did not result in consistent effectiveness and is not an FDA approved dose for CIU.

Eosinophilic Granulomatosis with Polyangiitis

mepolizumab (Nucala) versus placebo

A 52-week placebo-controlled trial randomized 136 adults with EGPA to receive mepolizumab 300 mg or placebo SC every 4 weeks while continuing on their stable oral corticosteroid (OCS) therapy, with or without immunosuppressive therapy.[106,107] After week 4, OCS use was tapered based on the investigator's discretion. A patient was considered in remission if on < 4 mg/day of OCS and achieving a

BVAS score of zero. After 52 weeks, mepolizumab resulted in significantly more accrued weeks of remission compared to placebo (28% versus 3% of patients had ≥ 24 weeks of accrued remission, odds ratio, 5.9 [95% CI, 2.7 to 13]). A greater proportion of patients were in remission at both the 36 and 48 week timeframes with mepolizumab (odds ratio, 16.7 [95% CI, 3.6 to 77.6]) and were stables on < 4 mg/day of OCS at week 52 (odds ratio, 5.1 [95% CI, 2.5 to 10.4]). The annualized relapse rate was 1.14 with mepolizumab and 2.27 with placebo (rate ratio, 0.5; 95% CI, 0.36 to 0.7; p<0.001). The safety profile of mepolizumab was similar to that reported in previous studies.

META-ANALYSES

A systematic review used data from drug inception to February 2016 of randomized controlled trials that individually assessed the effectiveness in severe asthma treatment of omalizumab and mepolizumab.[108] A mean difference of 0.38 (95% CI, 0.21 to 0.55; p<0.0001) in the Asthma Quality of Life Questionnaire (AQLQ) that favored omalizumab was found; however, the difference did not reach the minimal clinically important difference of 0.5. Similar improvements in Asthma Control Questionnaire, FEV_1, and Peak Expiratory Flow Rate (PEFR) were seen with both agents. Both agents achieved approximately a 50% reduction in the calculated annualized rates of asthma exacerbations compared to placebo.

A meta-analysis included 13 randomized controlled trials (n=6,000) comparing mepolizumab, reslizumab, and benralizumab versus placebo in adults and children with severe eosinophilic asthma as an adjunct to standard of care.[109] All agents reduced rates of clinically significant asthma exacerbation (defined by treatment with systemic corticosteroids for ≥ 3 days) by approximately half. Limited evidence for improved health-related quality of life scores (Asthma Control Questionnaire [ACQ] and Asthma Quality of Life Questionnaire [AQLQ]) and lung function (FEV_1) were found. No serious adverse events were reported with any of the agents. There was also no difference compared to placebo regarding discontinuation due to adverse effects with mepolizumab or reslizumab, but there were significantly more discontinuations of benralizumab than placebo, although the absolute numbers were small (36/1,599 benralizumab versus 9/998 placebo). While all 3 agents markedly reduced blood eosinophils, benralizumab resulted in almost complete depletion; the impact of this on efficacy and/or safety are unclear. A network meta-analysis of these 3 agents did not find statistical superiority of 1 agent over another, although each has demonstrated a benefit in reduction of exacerbations in published clinical trials.[110] Similarly, another network meta-analysis that compared only reslizumab and mepolizumab also did not find superiority of 1 agent over another.[111]

A network meta-analysis included 26 randomized controlled trials (n=8,444) from drug inception to December 2017 with patients receiving asthma treatment with mepolizumab, benralizumab, reslizumab, dupilumab, tralokinumab, and lebrikizumab.[112] Development of lebrikizumab and tralokinumab, anti-IL-13 monoclonal antibodies, has been discontinued due to a mixture of positive and negative trial outcomes. All agents, except tralokinumab, were superior to placebo on changes in FEV_1, ACQ, and AQLQ. Dupilumab showed the greatest increase in FEV_1 compared to placebo, followed by reslizumab and benralizumab. Mepolizumab showed the greatest reduction in ACQ scores, while dupilumab and mepolizumab showed the greatest increase in AQLQ scores. Decreased asthma exacerbation rates were only significant for dupilumab and reslizumab (rate ratios, 0.37 [95% CI, 0.17 to 0.8; p<0.011] and 0.64 [95% CI, 0.53 to 0.78; p<0.001])

A network meta-analysis included 21 randomized clinical trials published between 2003 and 2017 with patients treated with anti-interleukin-5 monoclonal antibody therapy versus placebo.[113] Anti-IL-5 agents included mepolizumab, reslizumab, and benralizumab. Using placebo as the reference, there were no statistically significant differences in FEV_1, AQLQ scores, or risk of exacerbation between the 3 anti-IL-5 agents. Reslizumab had a significantly lower rate of adverse events compared to benralizumab; no other statistically significant differences in adverse events among the other comparisons were observed. Ranking analyses suggested that reslizumab had the greatest likelihood of improving FEV_1 and AQLQ scores and reducing adverse event rates, while mepolizumab had the lowest exacerbation risk.

SUMMARY

Benralizumab (Fasenra), dupilumab (Dupixent), mepolizumab (Nucala), and reslizumab (Cinqair) are interleukin antagonists (IL-4/13 or IL-5) indicated as add-on maintenance treatment of patients with severe asthma and with an eosinophilic phenotype. Dupilumab is also indicated in patients with asthma who are dependent on oral corticosteroids. Mepolizumab is indicated in patients as young as 6 years old, benralizumab and dupilumab are approved for use in asthma patients as young as 12 years, and reslizumab is only approved for use in adults. Omalizumab (Xolair) is an anti-IgE monoclonal antibody indicated to treat patients with moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.

Approximately 10% to 20% of patients with asthma in the US are in poor control. Patients with eosinophilic asthma generally have severe disease with high eosinophil levels in the blood and sputum despite treatment with glucocorticoids. The 2020 Global Initiative for Asthma (GINA) guidelines advise a stepwise approach to asthma management, adjusting treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects. Patients with severe allergic asthma with elevated immunoglobulin E (IgE) levels may benefit from omalizumab (anti-IgE) therapy (Evidence A), those with severe eosinophilic asthma may benefit from benralizumab, mepolizumab, or reslizumab (interleukin-5 [IL-5] antagonists) therapy (Evidence A), and those with severe eosinophilic/type 2 asthma or patients requiring maintenance oral corticosteroids may benefit from dupilumab (interkleukin-4 [IL-4] antagonist) therapy (Evidence A.

Subcutaneous mepolizumab and intravenous reslizumab are dosed every 4 weeks, subcutaneous (SC) benralizumab is dosed every 8 weeks (initially every 4 weeks for 3 dose), SC dupilumab is dosed every 2 weeks, and SC omalizumab is dosed every 2 or 4 weeks for asthma. All 5 agents can cause hypersensitivity reactions, including anaphylaxis, and should be administered by a healthcare provider (HCP) or used under the guidance of an HCP (benralizumab, dupilumab, and mepolizumab); patients should be carefully monitored for an appropriate time period after the completion of the dose. Benralizumab (prefilled autoinjector only), dupilumab (prefilled syringe), and mepolizumab (prefilled autoinjector and syringe) and are available in formulations allowing for self- or caregiver-administration with proper training.

Placebo-controlled clinical studies have demonstrated that treatment with benralizumab, dupilumab, mepolizumab, omalizumab, or reslizumab was associated with significant reductions in asthma exacerbations. In trials, benralizumab, dupilumab, and reslizumab led to improved airway obstruction

as revealed by improvement in forced expiratory volume in 1 second (FEV_1). Treatment with benralizumab, dupilumab, and mepolizumab were associated with a reduction in daily maintenance oral corticosteroids dosages while maintaining asthma control. There are no comparative trials among the agents in this class to suggest preference of 1 agent over another for the treatment of severe asthma.

Omalizumab (Xolair) is also indicated to treat patients as young as 12 years with chronic idiopathic urticaria (CIU) who remain symptomatic despite H_1 antihistamine treatment. Clinical studies report greatest improvement in itching and hives with omalizumab 300 mg SC every 4 weeks; the 75 mg dosage is not indicated in the treatment of CIU.

Mepolizumab (Nucala) also is approved for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome. The recommended dose is 300 mg SC every 4 weeks (administered as 3 separate 100 mg injections).

Dupilumab (Dupixent) also carried indications for moderate-to-severe atopic dermatitis in patients ≥ 6 years of age and in chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults.

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